Unusual Rearrangement of Some Cyclobutachromanols. Facile Formation of Benzo-1,3-dioxane Ring System of Averufin

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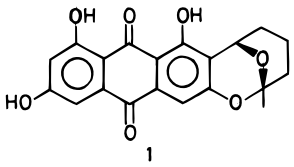
Acid-catalyzed rearrangement of cyclobutachromanol (**9**) furnished the benzo-1,3-dioxane **13**, arising from a de Mayo-type rearrangement. The structure of **13** was also proved by synthesis. Similarly, rearrangement of cyclobutachromanol **10** resulted in the benzo-1,3-dioxane compound **14**. The benzo-1,3-dioxane ring system is the characteristic structural feature of averufin, an intermediate in the biosynthesis of aflatoxins.

Introduction

The unique structural feature of averufin **1**,[1] the pivotal intermediate in the biogenetic pathway to aflatoxins, is the unusual presence of a benzo-1,3-dioxane ring system. Synthetic efforts[2] directed toward **1** have resulted in the development of various procedures for the assemblage of this internal ketal. We present here a facile entry to this ring system through a cyclobutyl carbinol rearrangement.[3] Previously, we had reported[4] the rearrangement of cyclobutachromanols **11** and **12** to provide a rapid synthesis of the marine sesquiterpenes aplysin **2** and filiformin **4** through an initial external bond migration. It had also been demonstrated that proper choice of solvents can dramatically control the initial step of the rearrangement. Herein we report an alternate mode of rearrangement in the case of cyclobutachromanols **9** and **10** that offers a ready access to the benzo-1,3-dioxane ring system of **1**.



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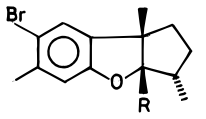
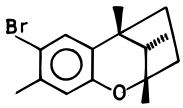


2: R = Me
3: R = CH_2OH



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Results and Discussion

Irradiation of a benzene solution of 2,7-dimethylchromone (**5**)[5] with continuous passage of ethylene furnished the cycloadduct **6** in 70% yield. The *cis* ring juncture of **6** followed from our previous studies.[4] This was alkylated with chloromethyl methyl ether using lithium diisopropylamide (LDA) as base and provided the methoxymethylated cyclobutachromanone **7** in 65% yield. The assignment of *cis* stereochemistry to the ring juncture in **7** was based on the following experiment. Methylation of **6** using LDA furnished the chromanone **8**, identical with a sample previously prepared by us.[4a] The cyclobutachromanone **7** was prepared since, following our earlier studies,[4a] this appeared most suited for a short synthesis of aplysinol (**3**) by way of rearrangement. Interaction of **6** and **7** with methylmagnesium iodide produced the cyclobutachromanols **9** and **10**, respectively, in 90% yield as single epimers, the homogeneity attested by their respective ^{1}H NMR spectra (Scheme 1). The configurational assignment of chromanols **9** and **10** is based on analogy with our earlier results.[4] The rearrangement of **9** and **10** was initially studied using BF_3·-Et_2O as catalyst. Thus, treatment of **9** in benzene with a catalytic amount of BF_3·Et_2O at ambient temperature followed by purification of the product by preparative TLC furnished a solid compound that was identified as the benzo-1,3-dioxane **13**. The structural assignment is based on detailed spectral studies. High-resolution mass spectrometry (218.1309) corresponded to a molecular formula of $C_{14}H_{18}O_2$. The compound in the ^{1}H NMR spectrum showed two singlets at δ 1.57 and 1.59 for three protons, each assignable to two quaternary methyl groups, a singlet at δ 2.28 for the aromatic methyl group, in addition to a six-proton multiplet at δ 1.5−2.0 and the three aromatic protons at δ 6.61−6.86. The ^{13}C NMR spectrum was more informative, and in combination with DEPT analysis the six aliphatic protons were identified as three methylene groups. Furthermore, the C-2 carbon flanked by two oxygen atoms appeared at δ 99.16, very close to the value for the same carbon in **1**.[6] All of the above data fit the assigned benzo-1,3-dioxane structure **13**. This was obtained in 70% yield and was the only isolated product. Confirmation for the assigned structure was obtained from synthesis. The synthesis was carried out following the previously reported procedure.[2] Thus,

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(2) (a) Roffey, P.; Sargent, M. V.; Knight, J. A. *J. Chem. Soc. C* **1967**, 2328. (b) Castonguay, A.; Brassard, P. *Can. J. Chem.* **1977**, *55*, 1324. (c) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Linc, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885. (d) Koreeda, M.; Hulin, B.; Yoshihara, M.; Townsend, C. A.; Christensen, S. B. *J. Org. Chem.* **1985**, *50*, 5426. (e) Townsend, C. A.; Davis, S. G.; Koreeda, M.; Hulin, B. *Ibid.* **1985**, *50*, 5428.

(3) Preliminary communication: Nath, A.; Mal, J.; Venkateswaran, R. V. *J. Chem. Soc., Chem. Commun.* **1993**, 1374.

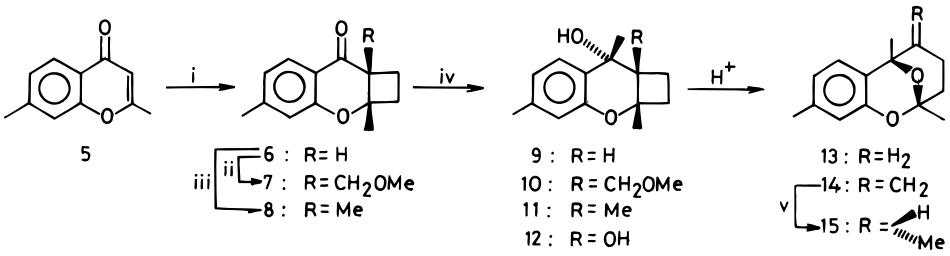
(4) (a) Nath, A.; Ghosh, A.; Venkateswaran, R. V. *J. Org. Chem.* **1992**, *57*, 1467. (b) Nath, A.; Venkateswaran, R. V. *J. Chem. Soc., Chem. Commun.* **1993**, 281. (c) Nath, A.; Mal, J.; Venkateswaran, R. V. *J. Org. Chem.* **1996**, *61*, 4391.

(5) Ganguly, B. K.; Bagchi, P. *J. Org. Chem.* **1956**, *21*, 1415.

(6) Townsend, C. A.; Christensen, S. B. *Tetrahedron* **1983**, *39*, 3575.

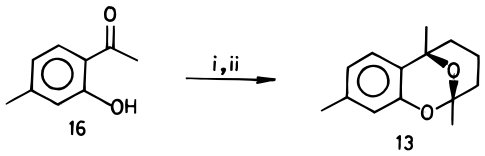
S0022-3263(96)01053-5 CCC: $12.00

Scheme 1[a]



[a] Reagents: (i) $CH_2{=}CH_2/h\nu$; (ii) LDA, $ClCH_2OMe$, THF; (iii) LDA, MeI, THF; (iv) MeMgI, Et_2O; (v) $Pd{-}C/H_2$.

Scheme 2[a]



[a] Reagents: (i) K, $MgCl_2$, 5-chloropentanone 2-ethylene ketal, THF; (ii) H^+.

2-hydroxy-4-methylacetophenone (**16**) was reacted with the Grignard reagent prepared from 5-chloropentanone 2-ethylene ketal and the product directly treated with acid. Purification of the reaction product afforded the benzo-1,3-dioxane **13** in 42% yield, arising from deketalization and concommitant internal ketalization (Scheme 2). Detailed efforts were not made to optimize the yield. The product obtained from rearrangement of **9** was identical in all respects (mp, spectra) with the sample synthesized above. The unusual formation of **13** by rearrangement may be visualized as arising through a de Mayo-type fragmentation[7] of the protonated chromanol **9** followed by hydroxy capture and internal ketalization (Scheme 3). Interestingly, no product from initial migration of the external or internal bond in the cyclobutachromanol **9** was seen. Even under the varying conditions of polar solvent and catalyst [(i) $BF_3{\cdot}Et_2O$ or sulfuric acid in petroleum ether at −78 °C, (ii) $BF_3{\cdot}Et_2O$ or sulfuric acid in nitroethane at −78 °C], which had remarkably altered the course of rearrangement in **11**,[4] the cyclobutachromanol **9** gave rise to only the benzo-1,3-dioxane **13** in yields ranging between 65 and 70%. Similarly, the cyclobutachromanol **10** on acid-catalyzed rearrangement under the conditions applied in case of **9** furnished exclusively the benzo-1,3-dioxane **14** in 60−70% yield as a crystalline solid. The structure of **14** was also deduced from detailed spectral analysis. A molecular formula of $C_{15}H_{18}O_2$ was indicated from HRMS. ^1H NMR showed the absence of the methoxymethyl group, and in its place two singlets at δ 4.77 and 5.03 assignable to the two hydrogens of the *exo*-methylene group were seen. By analogy with **13**, the quaternary carbon signal at δ 98.99 in the ^{13}C NMR of **14** could be assigned to C-2.

Additional support for the *exo*-methylene structure was obtained from hydrogenation. Catalytic hydrogenation of **14** furnished quantitatively the saturated compound **15**. The configuration of the secondary methyl group was assigned on the basis of greater accessibility to approach of hydrogen from the exo face in the dioxabicyclo[3.3.1]-nonane system. This addition results in the endo configuration for the methyl group, which places the methyl protons within the magnetic shielding cone of the benzene ring. In accordance with this, in the ^1H NMR spectrum of **15** the methyl group is shifted upfield and appeared at δ 0.76 ppm. The loss of the methoxy group leading to formation of **14** may be envisaged as arising from protonation at the methoxy oxygen in the putative de Mayo intermediate followed by an intramolecular displacement (Scheme 4). In one experiment a minor amount of a very polar compound was isolated that correspond to the ketone **17** on the basis of spectral considerations. This could have arisen by ring opening of the hemiacetal (path a, Scheme 4) and offered support for the proposed pathway in the rearrangement of the chromanols **9** and **10** to lead to benzo-1,3-dioxanes.

In conclusion, a novel and facile route to the benzo-1,3-dioxane ring system as present in averufin has been developed through acid-catalyzed rearrangement of cyclobutachromanols. The reason for the preference of cyclobutachromanols **9** and **10** to undergo exclusively a de Mayo-type fragmentation in sharp contrast to previous cases[4] is not immediately apparent. However, the pathway followed by these chromanols highlights the exciting possibilities in the rearrangement of cyclobutachromanols.

Experimental Section

General Procedures. All reactions were performed under an N_2 atmosphere. Melting points are uncorrected. Liquid products were subjected to bulb to bulb distillation, and the oven temperature is designated as ot. Solvents and reagents were reagent-grade materials and were further purified by conventional methods. 5-Chloro-2-pentanone ethylene ketal was obtained from Aldrich Chemicals. The petroleum ether that was used was that fraction of bp 60−80 °C and light petroleum ether of bp 40−60 °C. Preparative TLC was performed with silica gel 60 HF_{254} plates of 1-mm thickness. Na_2SO_4 was used to dry organic extracts.

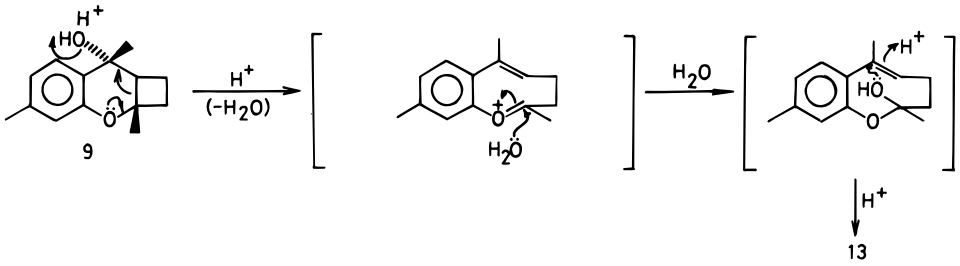
The IR spectra are of $CHCl_3$ solutions. ^1H NMR spectra of $CDCl_3$ solutions were recorded at 300 MHz and those of CCl_4 solutions at 60 MHz.

***cis*-1,2,2a,8a-Tetrahydro-2a,5-dimethyl-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8-one (6).** A solution of 2,7-dimethylchromone **5** (700 mg) in dry thiophene-free benzene (260 mL) was irradiated through a Pyrex filter with a Hanovia 450 W mercury lamp for 20 h, while ethylene was bubbled through the solution. Then the solvent was evaporated under reduced pressure and the residue was subjected to chromatography over silica gel. Elution with petroleum ether/EtOAc (49:1) afforded the photoadduct **6** as a colorless oil (570 mg, 70%): ot 110−120 °C (0.1 mmHg); IR 1665 cm^{-1}; ^1H NMR (CCl_4) δ 1.64 (s, 3H), 2.34 (s, 3H), 6.64 (br s, 1H), 6.73 (d, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.22; H, 6.93. Found: C, 77.20; H, 7.04.

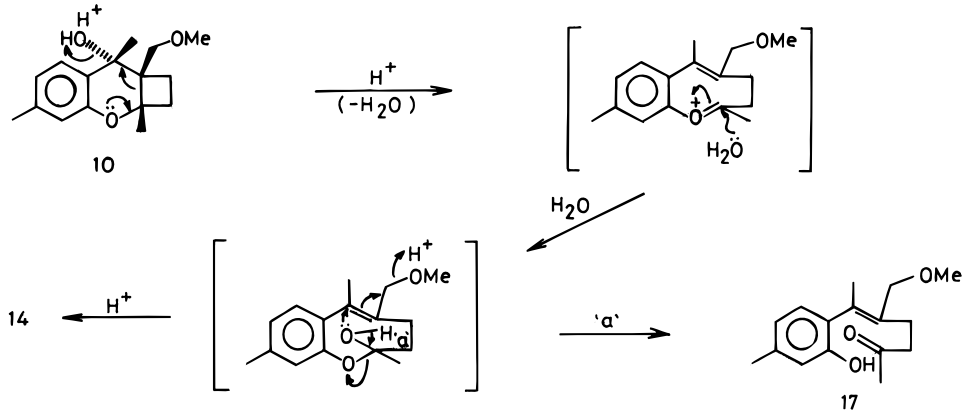
Further elution of the column with petroleum ether−EtOAc (4:1) furnished the starting chromone **5** (100 mg). On the basis of the recovered chromone the yield of the adduct **6** is 81%.

(7) Weedon, A. C. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: New York, 1984.

Scheme 3



Scheme 4



***cis*-1,2,2a,8a-Tetrahydro-2a,5-dimethyl-8a-(methoxymethyl)-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8-one (7).** To a well-stirred solution of LDA [prepared from nBuLi (1.5 mL, 1M, 1.5 mmol) and diisopropylamine (0.2 mL, 1.42 mmol)] in THF (15 mL) at −78 °C was added a solution of cyclobutachromanone **6** (270 mg, 1.33 mmol) in THF (5 mL) dropwise, and the reaction mixture was stirred for 30 min at the same temperature. Then chloromethyl methyl ether (0.1 mL, 1.33 mmol) was added through a syringe. The reaction mixture was stirred at −78 °C for 30 min, brought to rt, and further stirred for an additional 15 min. It was then decomposed with cold H_2O and extracted with Et_2O. The combined extracts were washed with dilute H_2SO_4 (2 N) and H_2O, dried, and concentrated. The residual oil was subjected to preparative TLC with petroleum ether/EtOAc (19:1). The less polar component, obtained as an oil, consisted of the starting material **6** (30 mg).

The more polar component, also an oil, was the desired alkylated product **7** [215 mg, 65% (73% based on recovered **6**)]: ot 90−95 °C (0.1 mmHg); IR 1665 cm^{-1}; ^1H NMR (CCl_4) δ 1.63 (s, 3H), 2.33 (s, 3H), 3.2 (s, 3H), 3.61 (q, J = 9 Hz, 2H), 6.66−6.83 (m, 2H), 8.06 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.17; H, 7.31. Found: C, 72.99; H, 7.25.

***cis*-1,2,2a,8a-Tetrahydro-2a,5,8a-trimethyl-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8-one (8).** Alkylation of cyclobutachromanone **6** was carried out as per the procedure for **7** using MeI as the alkylating agent. Yield of **8**, 120 mg (83%) from 130 mg of **6**. The product was found to be spectroscopically identical with the sample previously prepared.[4]

***cis*-1,2,2a,8a-Tetrahydro-2a,5,8-trimethyl-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8-ol (9).** To a magnetically stirred solution of MeMgI [prepared from Mg (50 mg, 0.002 g atom) and MeI (0.15 mL, 2.29 mmol) and dry Et_2O (15 mL)] at 0 °C was added a solution of **6** (210 mg, 1.03 mmol) in dry ether (5 mL). The reaction mixture was brought to rt and was stirred there for 15 min. Then it was refluxed for 30 min. It was then cooled to 0 °C and decomposed by adding saturated aqueous NH_4Cl. The two liquid layers were separated. The aqueous layer was extracted with ether. The combined organic layers were washed with water, dried, and concentrated to afford **9** as a colorless oil (200 mg, 90%): ^1H NMR (CCl_4) δ 1.33 (s, 3H), 1.5 (s, 3H), 2.31 (s, 3H), 6.6−6.76 (m, 2H), 7.34 (d, J = 8 Hz, 1H). This material was used in the next step without further purification.

***cis*-1,2,2a,8a-Tetrahydro-2a,5,8-trimethyl-8a-(methoxymethyl)-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8-ol (10).** This was prepared from the cyclobutachromanone **7** following the same procedure as for **9**. Yield, 200 mg (90%) from 210 mg of **7**: ^1H NMR (CCl_4) δ 1.27 (s, 3H), 1.34 (s, 3H), 2.26 (s, 3H), 3.4 (s, 3H), 3.79 (q, J = 9 Hz, 2H), 6.61−6.8 (m, 2H), 7.39 (d, J = 8 Hz, 1H). This was also used in the next step without further purification.

Acid-Catalyzed Rearrangement of Cyclobutachromanol 9. Method A. To a magnetically stirred solution of chromanol **9** (100 mg) in dry benzene at rt was added a drop of freshly distilled $BF_3{\cdot}Et_2O$ by means of a syringe. The mixture was stirred for 10 min, and then it was decomposed by adding saturated aqueous $NaHCO_3$. The two liquid layers were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed (saturated brine and water) and dried. Evaporation of the solvent and preparative TLC [petroleum ether/EtOAc (49:1)] of the residual oil afforded the benzo-1,3-dioxane **13** as a colorless solid (70 mg, 70%): mp 72−74 °C (light petroleum ether); ^1H NMR ($CDCl_3$) δ 1.53 (s, 3H), 1.59 (s, 3H), 1.5−1.8 (m, 5H), 1.9−2.0 (m, 1H), 2.28 (s, 3H), 6.61 (br s, 1H), 6.64 (d, J = 7.6 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.37, 21.14, 26.74, 28.47, 35.60, 37.35, 73.41, 99.16, 115.33, 120.32, 123.43, 137.98, 153.17; m/z 218.1309 ($C_{14}H_{18}O_2$).

Method B. To a magnetically stirred solution of chromanol **9** (100 mg) in dry petroleum ether (10 mL) at −78 °C was added a drop of concentrated H_2SO_4 by means of a syringe. The reaction mixture was stirred at −78 °C for 30 min and then was allowed to warm to rt and was decomposed by adding saturated aqueous $NaHCO_3$. Et_2O was then added. The two liquid layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water, dried, and concentrated. The residual oil was purified by preparative TLC [petroleum ether/EtOAc (49:1)] and furnished the benzo-1,3-dioxane **13** (65 mg, 65%), which was identical (mp, ^1H NMR) to a sample prepared by method A.

Method C. To a magnetically stirred solution of chromanol **9** (100 mg) in dry $EtNO_2$ (10 mL) at −78 °C was added a drop of concentrated H_2SO_4 by means of a syringe. After 30 min of stirring at −78 °C, the reaction mixture was allowed to warm to rt and was decomposed by adding saturated aqueous $NaHCO_3$. Et_2O was added, and the two liquid layers were

separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with water, dried, and concentrated. The residual oil was purified by preparative TLC [petroleum ether/EtOAc (49:1)] to afford the benzo-1,3-dioxane **13** (70 mg, 70%). This was identical (mp, ^{1}H NMR) with a sample prepared by method A.

Synthesis of the Benzo-1,3-dioxane 13. Activated magnesium was prepared by heating to reflux for 3 h anhydrous magnesium chloride (600 mg, 6.4 mmol) in dry THF (10 mL) in the presence of potassium metal (500 mg, 12.7 mmol). After the mixture was cooled to rt, 5-chloro-2-pentanone ethylene ketal (500 mg, 3 mmol) was added, the reaction mixture stirred at rt for 4 h, and then 2-hydroxy-4-methylacetophenone **16** (150 mg, 1 mmol) was added dropwise by a syringe. The reaction mixture was stirred at rt for 1 h and refluxed for 12 h. It was then cooled to rt and quenched by addition of cold water. It was then acidified with cold dilute HCl (2 N), stirred at ambient temperature for 1 h, and extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and water, dried, and concentrated. The residual oil was subjected to preparative TLC [petroleum ether/EtOAc (49:1)] to afford the benzo-1,3-dioxane **13** (55 mg, 25%). This was found to be identical (mp, ^{1}H NMR) with the sample of **13** obtained by rearrangement of **9**.

From the base layer in the preparative TLC was obtained, after further purification by preparative TLC [petroleum ether/EtOAc (9:1)] the recovered acetophenone **16** (60 mg). On the basis of recovered **16**, the yield of **13** was 42%.

Acid-Catalyzed Rearrangement of Cyclobutachromanol (10). The chromanol **10** was subjected to acid catalyzed rearrangement under the various conditions (methods A−C) employed in the case of the chromanol **9**. In all cases the reaction afforded the benzo-1,3-dioxane **14** in yields ranging between 60 and 70%. The product obtained as an oil eventually, solidified on keeping in the refrigerator and was crystallized from ether−light petroleum ether: mp 58−59 °C; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3H), 1.72 (s, 3H), 1.85−2.0 (m, 1H), 2.27 (s, 3H), 2.05−2.4 (m, 3H), 4.77 (s, 1H), 5.03 (s, 1H), 6.63 (s, 1H), 6.64 (d, J = 6.8 Hz, 1H), 6.86 (d, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.13, 23.55, 27.07, 27.96, 38.03, 74.88, 98.99, 106.59, 115.86, 120.64, 123.36, 123.87, 138.26, 148.59, 152.47; m/z 230.1305 ($C_{15}H_{18}O_2$).

In one experiment using method A, a minor amount (ca. 15 mg) of a very polar product was also isolated in addition to the desired product **14** in a lower yield. This has been assigned the open-chain structure **17** from spectral considerations: ^{1}H NMR (CCl_4) δ 1.96 (s, 3H), 2.26 (s, 6H), 3.33 (s, 3H), 4.03 (s, 2H), 6.4−6.9 (m, 3H).

Hydrogenation of 14. The alkene **14** (50 mg) was hydrogenated in the presence of 10% Pd−C (5 mg) in double-distilled ethanol (5 mL) under atmospheric pressure. After 3 h, the catalyst was filtered off and the filtrate was concentrated under reduced pressure to afford **15** as a colorless oil (50 mg, 99%): ot 100−110 °C (1 mm Hg); ^{1}H NMR (CCl_4) δ 0.76 (d, J = 8 Hz, 3H), 1.43 (s, 3H), 1.46 (s, 3H), 2.26 (s, 3H), 6.4−6.6 (br, 2H), 6.76 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.28; H, 8.58.

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